C–C Bond Formation by Radical Cyclization: Synthesis of Pyrimidine-Annulated Heterocycles

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Abstract: A number of pyrimidino[3,2-c]tetrahydroisoquinolin-2,4-diones are synthesized in excellent yields from 1,3-dialkyl-5-(N-2'-bromobenzyl,N-methyl)aminopyrimidine-2,4-diones by intramolecular addition of aryl radical to the uracil ring bearing the amino nitrogen atom. Usual aerial oxidation in this type of cyclization with Bu3SnH is not observed in the present instance.

Key words: pyrimidine, heterocycles, radical cyclization, organotin reagent, 6-endo-trig

Aryl radical cyclization has recently emerged as a valuable tool in organic synthesis.1 The Bu3SnH/AIBN-induced radical cyclization has been applied for the synthesis of various heterocyclic compounds.2 Literature reveals several examples of heteroaryl radicals. Examples by Snieckus3a,b,4a and Harrowven,4b,c involve pyridine and pyridyl radicals. An example of an indonyl radical5a,b was reported by Sundberg5c in the synthesis of Iboga alkaloids. The cyclization of radicals derived from N-(o-bromobenzyl)anilines to phenanthridine has been reported.6 The cyclization of aryl radical usually has a 5-exo:6-endo ratio indicating a stronger preference for exo-cyclization than alkyl radicals. But for stabilized radicals7–9 this preference is reversed. This is exemplified by the radical cyclization of N-(o-bromobenzyl)enamide precursors which exclusively undergo ‘6-endo-trig’ cyclization to afford the tetrahydroisoquinolone derivatives via the stable α-aminoalkyl radical intermediate.7

The importance of pyrimidine and its derivatives are well known. Some derivatives are active against cancer,10 viral diseases11–14 and AIDS virus.15 Functionalization of uracil at the C-511,16–19 and C-620–22 leads to biologically interesting molecules, but it is not a simple task, requiring rather sophisticated and tedious reaction conditions.23–25 We have recently reported the synthesis of a number of pyrimidine-annulated heterocycles by [3,3] sigmatropic rearrangements.26 Continuation of our endeavor to synthesize new heterocycles27 prompted us to study the aryl radical cyclization for the synthesis of pyrimidine-annulated heterocyclic compounds. Herein we report the results.

The amines 4a–f required for the present study were readily prepared in 90–96% yield from o-bromobenzyl bromides 3a, b and 1,3-dialkyl-5-N-methylaminopyrimidine-2,4-diones 2a–c by refluxing in acetone for 6–8 hours in the presence of anhydrous potassium carbonate and potassium iodide (Scheme 1).

As our aim was to synthesize pyrimidine-annulated heterocyclic compounds from the substrates 4a–f, we have therefore examined the scope for C–C bond formation in this system by Bu3SnH/AIBN-induced radical cyclization methodology. Compound 4a when heated with tributyltin chloride, sodium cyanoborohydride and AIBN in refluxing degassed benzene under nitrogen for 5 hours, afforded the product in 85% yield. The structure of the product 5a was established from its elemental composition and analysis of the 1H

Scheme 1 Reagents and conditions: i) 40% aq MeNH2, reflux, 1 h; ii) K2CO3, acetone, NaI, reflux, 6–8 h
NMR spectrum. Compound \(5a\) displayed one proton doublet at \(\delta = 3.83\) \((J = 6\ \text{Hz})\) and another proton doublet at \(\delta = 4.55\) \((J = 6\ \text{Hz})\) due to ring junction protons \(H_a\) and \(H_b\), respectively. The two NCH\(2\) protons appear as two proton doublet each at \(\delta = 3.89\) and 4.13 \((J=16\ \text{Hz})\). The \(^{13}\text{C}\) NMR spectrum of \(5a\) also strongly supported its structure. The \(^{13}\text{C}\) chemical shift of compound \(5a\) was assigned by DEPT experiment. Multiplicity is established by DEPT experiments and show eleven protonated carbons, three CH\(_3\), two CH\(_2\), and six CH moities. The mass spectrum of compound \(5a\) showed a molecular ion peak at \(m/z = 273\) \((M^+)\). The other substrates \(4b-f\) were also treated similarly with Bu\(_3\)SnCl, NaBH\(_3\)CN and AIBN to give exclusively the tetrahydropyridine derivatives \(5b-f\) in 80–85\% yields (Scheme 2).

The formation of six-membered heterocyclic ring in products \(5a-f\) from the substrates \(4a-f\) may be easily explained by the initial formation of the aryl radical 6 followed by a '6-endo' ring closure to give a tertiary radical 9 which may then accept a hydrogen radical to afford the final products \(5a-f\). In an alternative route, the aryl radical 6 may undergo a '5-exo' ring closure to generate a spiroheterocyclic radical 7 which may be converted to the tertiary radical 9 via radical 8 by a neophyl rearrangement (Scheme 3).

One interesting observation is that the usual oxidation does not occur at the present instance and the dihydro compound is isolated in excellent yield. The usual course during this type of cyclization is that the initially formed dihydro products give oxidized products by aerial oxidation, i.e., an oxidation step in Bu\(_3\)SnH-mediated cyclization. The reaction has shown to be a general one. All the six substrates gave regioselectively the six-membered tetrahydropyridine rings. The methodology is simple and affords the pyrimidino[3,2-c]tetrahydroisoquinolin-2,4-diones in excellent yields.

Melting points were determined in an open capillary and are uncorrected. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401 PC spectrophotometer (\(\lambda_{max}\) in nm) and IR spectra were recorded on a Perkin Elmer L120-000A grating IR spectrophotometer and the frequency is reported in cm\(^{-1}\). \(^1\text{H}\) NMR (300 MHz) and \(^{13}\text{C}\) NMR (75.5 MHz) spectra were recorded in CDCl\(_3\) on a Bruker DPX-300 instrument at the Indian Institute of Chemical Biology, Kolkata (chemical shift in \(\delta\)) spectrometer using TMS as an internal standard. Elemental analyses and recording of mass spectra were carried out by RSIC(CDRI) Lucknow on a Jeol D-300 (El) instrument. Silica gel (60–120 mesh, Spectrochem, India) was used for chromatographic separation. Petroleum ether refers to the fraction boiling between 60 and 80 °C.
1,3-Dialkyl-5-(N-2'-bromobenzyloxy-N-methylaminopyrimidine-2,4-diones 4a–f; General Procedure

A mixture of 5-methylamionaurici 2a–c (5 mmol), 2-bromobenzyl bromide 3a (5 mmol) or 2-bromo-5-methoxybenzyl bromide 3b (4 mmol), anhyd K$_2$CO$_3$ (5 g) and NaI (50 mg) was refluxed in anhyd acetone (125 mL) on a water-bath for 6–8 h. The reaction mixture was then cooled, filtered, and the solvent was removed. The residual mass was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined CH$_2$Cl$_2$ extracts were washed with H$_2$O and dried (Na$_2$SO$_4$). The residual mass after removal of the solvent was subjected to column chromatography over silica gel using petroleum ether–EtOAc (4:1) as eluent to give compounds 4a–f as viscous liquids.

4a

Yield: 94%.

IR (neat): 753, 1450, 1652, 1699, 2978 cm$^{-1}$.

1H NMR (CDCl$_3$, 300 MHz): δ = 1.22 (t, J = 7 Hz, 3 H, NCH$_2$CH$_3$), 2.65 (s, 3 H, NCH$_3$), 3.34 (s, 3 H, NCH$_3$), 3.40 (q, J = 7 Hz, 2 H, NCH$_2$CH$_3$), 4.25 (s, 2 H, NCH$_2$), 6.60 (s, 1 H, =CH), 7.09 (m, 2 H, ArH), 7.52 (m, 2 H, ArH).

MS: m/z = 351, 353 (M$^+$.)

UV (EtOH): λ$_{max}$ = 304, 211 nm.

Anal. Calcd for C$_{17}$H$_{22}$BrN$_3$O$_3$: C, 50.41, H, 5.67, N, 11.28.

Yield: 85%; white solid; mp 140 °C.

4c

Yield: 96%.

IR (neat): 750, 1465, 1651, 1698, 2978 cm$^{-1}$.

1H NMR (CDCl$_3$, 300 MHz): δ = 0.78 (t, J = 7 Hz, 3 H, NCH$_2$CH$_3$), 2.66 (s, 3 H, NCH$_3$), 3.35 (s, 3 H, NCH$_3$), 3.38 (s, 3 H, NCH$_3$), 4.24 (s, 2 H, NCH$_2$), 6.63 (s, 1 H, =CH), 6.67 (dd, J = 3, 9 Hz, 1 H, ArH), 7.13 (d, J = 3 Hz, 1 H, ArH), 7.39 (d, J = 9 Hz, 1 H, ArH).

MS: m/z = 381, 383 (M$^+$.)

UV (EtOH): λ$_{max}$ = 304, 210 nm.

Anal. Calcd for C$_{17}$H$_{28}$BrN$_3$O$_3$: C, 50.41, H, 5.40, N, 10.82.

4d

Yield: 95%.

IR (neat): 752, 1469, 1651, 1698, 2944 cm$^{-1}$.

1H NMR (CDCl$_3$, 300 MHz): δ = 7.20 (t, J = 7 Hz, 3 H, NCH$_2$CH$_3$), 7.21 (t, J = 7 Hz, 3 H, NCH$_2$CH$_3$), 2.91 (s, 3 H, NCH$_3$), 3.42 (s, 3 H, NCH$_3$), 3.56 (q, J = 7 Hz, 2 H, NCH$_2$CH$_3$), 3.83 (d, J = 6 Hz, 1 H, CCH), 3.89 (d, J = 16 Hz, 1 H, CCH), 4.13 (d, J = 16 Hz, 1 H, CCH), 4.55 (d, J = 6 Hz, 1 H, CCH), 7.06 (m, 4 H, ArH).

UV (EtOH): λ$_{max}$ = 273, 206 nm.


1,3-Dialkylpyrimidino[3,2-c]tetrahydroisoquinolin-2,4-diones 5a–f; General Procedure

A suspension of 4a–f (0.08 mmol), Bu$_2$SnCl (0.08 mL, 0.296 mmol), NaBH$_4$,CN (250 mg, 3.98 mmol) and AIBN in degassed anhyd benzene (8 mL) was refluxed for 5 h under N$_2$. The solvent was evaporated under reduced pressure, the residue was taken in H$_2$O (10 mL), and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were washed with 1% aq Na$_2$SO$_4$ and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent furnished the residual mass which was then magnetically stirred with a sat. aq solution of KF for 24 h. It was then extracted with CH$_2$Cl$_2$ (3 × 10 mL), the combined CH$_2$Cl$_2$ layers were washed several times with H$_2$O and dried (Na$_2$SO$_4$). The residual mass after removal of the solvent was subjected to column chromatography using petroleum ether–EtOAc (3:1) as eluent to give cyclized products 5a–f which were then recrystallized from CH$_2$Cl$_2$–petroleum ether.
Synthesis of Pyrimidine-Annulated Heterocycles

5b
Yield: 80%; white solid; mp 150 °C.
IR (KBr): 1465, 1671, 1712, 2924 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 0.83 (t, J = 7 Hz, 3 H, NCH₂CH₃), 1.32 (t, J = 7 Hz, 3 H, NCH₂CH₃), 2.93 (s, 3 H, NCH₃), 3.25 (q, J = 7 Hz, 1 H, NCH(CH₃)₂), 3.55 (q, J = 7 Hz, 2 H, NCH₂CH₃), 3.75 (d, J = 6 Hz, 1 H, CCH), 3.86 (d, J = 16 Hz, 1 H, NCH), 4.13 (d, J = 16 Hz, 1 H, NCH), 4.34 (q, J = 7 Hz, 1 H, NCH₃CH₂NCH₃), 4.59 (d, J = 6 Hz, 1 H, CCH), 7.06 (m, 4 H, ArH).

MS: m/z = 298 (M⁺).

UV (EtOH): λₘₐₓ = 273, 205 nm.

5c
Yield: 83%; white solid; mp 138 °C.
IR (KBr): 1471, 1668, 1719, 2932 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 2.92 (s, 3 H, NCH₃), 2.95 (s, 3 H, NCH₃), 3.34 (s, 3 H, NCH₃), 3.77 (s, 3 H, OCH₃), 3.80 (d, J = 16 Hz, 1 H, NCH), 3.85 (d, J = 6 Hz, 1 H, CCH), 4.13 (d, J = 16 Hz, 1 H, NCH), 4.57 (d, J = 6 Hz, 1 H, CCH), 7.07 (m, 4 H, ArH).

MS: m/z = 259 (M⁺).

UV (EtOH): λₘₐₓ = 273, 206 nm.

5d
Yield: 84%; white solid; mp 152 °C.
IR (EtOH): λₘₐₓ = 259, 200 nm.

1H NMR (CDCl₃, 300 MHz): δ = 2.81 (s, 3 H, NCH₃), 2.96 (s, 3 H, NCH₃), 3.41 (s, 3 H, NCH₃), 3.77 (s, 3 H, OCH₃), 3.80 (d, J = 16 Hz, 1 H, NCH), 3.85 (d, J = 6 Hz, 1 H, CCH), 4.10 (d, J = 16 Hz, 1 H, NCH), 4.11 (d, J = 16 Hz, 1 H, NCH), 4.31 (q, J = 7 Hz, 1 H, NCH₃CH₂NCH₃), 4.51 (q, J = 7 Hz, 1 H, NCH₃CH₂NCH₃), 5.45 (d, J = 6 Hz, 1 H, CCH), 6.57 (dd, J = 2 Hz, 1 H, ArH), 7.11 (d, J = 9 Hz, 1 H, ArH).

MS: m/z = 317 (M⁺).

UV (EtOH): λₘₐₓ = 274, 206 nm.

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References


